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CASE REPORT

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Perforated Cecal Mucinous Adenocarcinoma with Heterotopic Ossification: A Case Report

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Abstract

Heterotopic ossification, also termed osseous metaplasia, is a known pathological condition of bone formation in extraskeletal sites. Its widespread occurrence in tumors is infrequent and the presentation in neoplasms of the gastrointestinal tract is very rare. Previous studies described different subtypes of benign and malign gastrointestinal tumors exhibiting areas of stromal osseous metaplasia. The relevance of its presence in the stroma of epithelial tumors, as well as the pathogenesis, remains still unknown. We report a case of mucinous carcinoma with osseous metaplasia. The tumor was located in the cecum and was composed of atypical epithelial glands, pools of extracellular mucin, calcifications, necrosis, and stromal osseous metaplasia. Metaplastic bone fragments histologically displayed a benign appearance. The tumor was staged as advanced and presented with perforation. Perforated colorectal carcinoma is frequently presented as an emergency case, and prompt surgical management is imperative. **(International Journal of Biomedicine. 2024;14(3):532-535.)**

Keywords: heterotopic ossification • osseous metaplasia • cecal carcinoma • mucinous adenocarcinoma • tumor perforation

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Introduction

Heterotopic ossification, also termed osseous metaplasia, is a pathological condition that implies the formation of bony tissue outside the skeletal system. Heterotopic ossification is described in several circumstances of non-neoplastic conditions, like traumatic heterotopic ossification, as well as in neoplastic conditions.[1]

Mature bone formation in tumor stroma is a rare event encountered sporadically in the neoplasm of organs such as the lung, kidney, and breast.[2,3,4] It is also described as an unusual occurrence in benign and malignant neoplasms of the gastrointestinal tract.[5,6] Though colorectal carcinoma is among the most common carcinoma of the gastrointestinal tract, tumor stroma ossification is rarely described. To date, the most common localization of heterotopic ossification in colorectal carcinoma was described in the rectum. The circumstances of its formation and pathogenesis are poorly understood; it is considered an innocuous aspect of carcinoma with unknown prognostic consequences.[7]

Herein, we report the clinicopathological features and immunohistochemical findings of a case of perforated mucinous adenocarcinoma localized in the cecum containing areas of stromal osseous metaplasia.

Case Presentation

We present a case of a 25-year-old male who was admitted to the surgery department of the University Clinical Center in Prishtina with symptoms of acute gastrointestinal obstruction, presenting with unbearable pain in the lower right quadrant of the abdomen and distension. The CT native scan revealed the presence of air-fluid levels in the region of the ascending colon, while an irregular hyperdense mass was located in the cecum. The patient underwent surgery, right hemicolectomy, with additional regional lymph node resection. Primary ileo-transverse T-T anastomosis, peritoneal lavage, and drainage were undertaken.

The resected specimen, with a length of 35 cm, comprised the cecum, ileocecal valve, and ascending colon.

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The gross examination of the surgical specimen uncovered an exophytic fungating mass measuring 5 cm in greatest diameter, white to grayish in color, and moderate to hard/osseous in consistency. The tumor mass was located at the upper part of the cecum, near the ileocecal valve. On the cut surface, the tumor extended through the entire colonic wall at the depth of serosa, causing perforation. The involved colonic wall grossly showed multifocal necrotic and hemorrhagic areas.

Microscopically, the neoplastic mass comprised atypical glands of different sizes and mucin-filled, lying in the mucosa and invading the entire colonic layers. The extracellular pools of mucin were abundantly observed, exceeding 50 % of tumor mass (Figure 1: A, C, E, F). Along with the mucin pools of neoplastic stroma, numerous calcifications were observed (Figire 1D), which were detected as basophilic granules, clusters, and sheets. Bone fragments of different sizes were observed in the tumor stroma, close to mucin pools (Figure 1. A, B). Prominent inflammation, hemorrhage, necrosis, and perforation were observed in the colon within the tumor mass (Figure 1F). There were no vascular or lymphatic invasions of tumor cells. Identified lymph nodes in the resected colon specimen showed no tumor cells or heterotopic ossification.

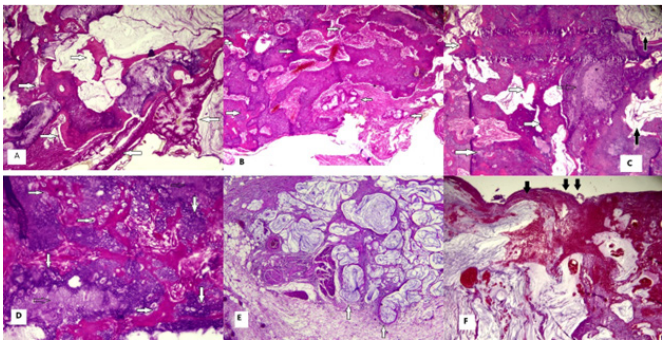

Figure 1. *Morphological appearance of cecal mucinous adenocarcinoma in H&E staining.* ***A***, ***B****. Areas of tumor stromal osseous metaplasia in the background of mucin and calcification (bone fragments, right arrows), malignant glands in the vicinity of bone fragments (left arrows) (Original Magnification 40x).* ***C****. Necrotic areas within ossified tumor component (empty arrow), extracellular mucin (black arrows), bone spicules (right arrows).* ***D****. Necrotic areas (empty arrows) surrounded with calcification (vertical arrows) and bone spicules (right arrows).* ***E****. Abundant extracellular mucin invading through all bowel wall layers (arrow)* ***F****. Prominent areas of hemorrhage and necrosis indicate tumor site perforation (black arrows).*

Immunohistochemical staining was performed to characterize the tumor cells further. Neoplastic cells showed positivity for CKAE1/AE2 (Figure 2A), B-catenin (Figure 2B), and CK20 (Figure 2C). Immunostaining for Ki67 (Figure 2D) showed a high proliferation index. Tumor cells showed negativity for CK7 and p53 (data not shown). Further evaluation of tumor cells was performed using a four-antibody panel for MMR protein expression. The tumor cells showed weak staining for MLH1. We could not determine the mismatch repair (MMR) or microsatellite instability (MSI) status by polymerase chain reaction analysis because our institution does not provide this assay. No mutation was detected in *BRAF V600E*. The case was diagnosed as perforated cecal mucinous adenocarcinoma with heterotopic ossification, pT4 N0- stage III.

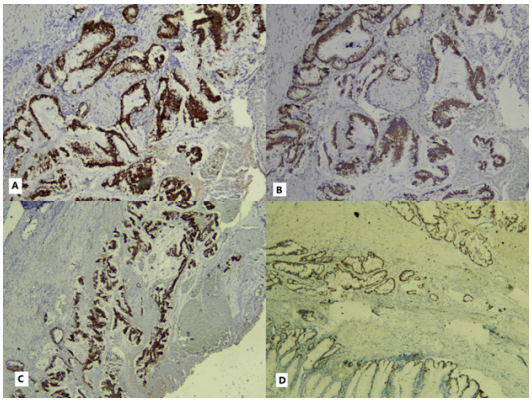

Figure 2. *Immunohistochemical tumor profile.* ***A****. Positive immunostaining for CK AE1/AE3 in tumor cells (original magnification 40x).* ***B****. Positive immunostaining for B-catenin in tumor cells (original magnification 40x).* ***C****. Positive immunostaining for CK20 in tumor cells (original magnification 20x).* ***D****. Expression of Ki-67 showing a high proliferation index in tumor cells and positive reactive expression in epithelia (original magnification 20x).*

Discussion

Heterotopic ossification or osseous metaplasia is a rare phenomenon in the gastrointestinal tract, reported as an incidental finding present in benign and malign appendiceal and colorectal neoplasms.[5,7,8] It is associated with primary or secondary tumor masses involving metastatic regional lymph nodes or distant tissues and organs.[9,10] According to Dukes, the estimated frequency of heterotopic ossification in rectal cancer is less than 0,4%.[11] Heterotopic ossification in cecal adenocarcinoma is infrequently described. To our knowledge, the present case is the third reported case of mucinous cecal adenocarcinoma in the English literature, presented clinically as a surgical emergency case at a younger age than has been reported so far.

In the previous case reports of colorectal cancer with heterotopic ossification, the main patient complaints were changed bowel habits, constipation or diarrhea, hematochezia, and secondary anemia. None of the reported cases presented clinically with acute abdominal pain and signs of colon tumor perforation. Tumor perforation is a rare manifestation of colorectal cancer, with the incidence ranging from 3-10%.[12] Usually, the perforation locus is observed at the site of tumor localization or proximal to it. Perforation in the cancer site occurs due to tumor ischemia and necrosis.[12,13] Meanwhile, proximal perforation refers to diastatic perforation of the colon upward from obstructing the tumor mass.[14] In the presented case, diffuse areas of hemorrhage and necrosis were grossly and microscopically observed within the tumor mass, suggesting tumor site perforation (Figure 1F). Cecal anatomy,

as a segment of the large intestine with a blind ending, favors inflammatory and necrotic changes due to fecal entrapment distal to the tumor, while the intestine passage is not impaired totally. However, the mechanical stress of bone fragments in tumor stroma and mucinous background may have contributed to the progression of tumor invasiveness. Tumor perforation is associated with an advanced tumor stage and a worse prognosis due to a higher postoperative mortality rate and risk of tumor cell spillage in the peritoneal cavity.[15] The current treatment strategy is emergency surgery with resection and primary ileo-colic anastomosis.[13]

The current cecal adenocarcinoma case is characterized by an extracellular mucinous component that exceeds 50% of the tumor (Figure 1. A, C, E, F), categorizing it as mucinous adenocarcinoma. This unique histological subtype of colorectal cancer is more commonly described in the proximal colon. Noteworthy, mucin-producing tumors are the most reported cases of colorectal carcinoma associated with heterotopic ossifications,[7,8] whereas its role in the histogenesis of osseous metaplasia is not clarified. According to Van Patter, an important role in initiating stromal ossification is the interaction of calcium salt deposits within the mucinous setting.[16] Similarly, the calcium basophilic deposits were closely associated with mucin layers and bone fragments (Figure 1D). This observation favors the role of calcium aggregates for bone formation in tumors with mucinous backgrounds. Besides mucin deposits, other circumstances like necrosis [11] and inflammation[6] are consistently found in neoplasms with heterotopic ossification. These surrounding neoplastic components are suggested as microenvironmental factors responsive to osteogenic differentiation.[16] To date, the most supported mechanism of tumor ossification is osteoblastic metaplasia of pluripotent mesenchymal stromal cells.[17] The initiation of mesenchymal cell differentiation into osteoblasts is influenced by osteoinductive factors generated by the cancer cells, potentially the bone morphogenetic proteins.[17] Previous studies showed immunohistochemical expression of different types of bone morphogenetic proteins (BMP) in the cancer cells close to foci of stromal ossification, suggestive of their role in metaplastic bone formation.[16,17,18] According to current knowledge, bone morphogenetic proteins play an important role in tumor progression and invasiveness.[19]

Because of similar clinical presentation, colorectal carcinoma with heterotopic ossification must be differentiated from carcinosarcoma. Microscopically, both histopathologic entities are composed of mesenchymal and epithelial elements. Mesenchymal components have a histologically benign appearance resembling normal bone tissue. But, in the case of carcinosarcoma, the sarcomatous component shows different types of sarcomatous differentiation resembling chondrosarcoma, osteogenic sarcoma, or unspecific spindle cell sarcoma.[19] This distinction is relevant for prognostic significance and therapeutical issues.

In conclusion, cecal mucinous adenocarcinoma with osseous metaplasia is a rare occurrence. This rare combination demonstrates diagnostic complexity, and we emphasize the need to raise awareness of this phenomenon. Bone metaplasia, despite its innocuous appearance, when localized in the cecum, carries a risk of perforation with prognostic consequences, so it should be considered.

Ethical Considerations

The patient provided written informed consent to publish case-associated data and accompanying images without identifying details.

Competing Interests

The authors declare that they have no competing interests.

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